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Recommendations and Reports

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Sexually Transmitted Diseases Treatment Guidelines, 2010

to support the use of ceftriaxone for the treatment of congenital syphilis. Therefore, ceftriaxone should be used in consultation with a specialist in the treatment of infants with congenital syphilis. Management may include a repeat CSF examination at age 6 months if the initial examination was abnormal.

2. For infants without any clinical evidence of infection (Scenario 2 and Scenario 3), use
 - a. procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days;
 - or
 - b. benzathine penicillin G, 50,000 U/kg IM as a single dose.

If any part of the evaluation for congenital syphilis is abnormal, CSF examination is not interpretable, CSF examination was not performed, or follow-up is uncertain, procaine penicillin G is recommended. A single dose of ceftriaxone is inadequate therapy.

3. For premature infants who have no other clinical evidence of infection (Scenario 2 and Scenario 3) and might not tolerate IM injections because of decreased muscle mass, IV ceftriaxone can be considered with careful clinical and serologic follow-up (see Penicillin Shortage, Number 1). Ceftriaxone dosing must be adjusted according to age and birth weight.

HIV Infection

Evidence is insufficient to determine whether infants who have congenital syphilis and whose mothers are coinfecting with HIV require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants.

Management of Persons Who Have a History of Penicillin Allergy

No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. Penicillin also is recommended for use, whenever possible, in HIV-infected patients. Of the adult U.S. population, 3%–10% have experienced an immunoglobulin E (IgE)-mediated allergic response to penicillin (238,239), such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension). Readministration of penicillin to these patients can cause severe, immediate reactions. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic patients, unless they undergo acute desensitization to eliminate anaphylactic sensitivity.

Although an estimated 10% of persons who report a history of severe allergic reactions to penicillin continue to remain

allergic their entire lives, with the passage of time, most persons who have had a severe reaction to penicillin stop expressing penicillin-specific IgE (238,239). These persons can then be treated safely with penicillin. Penicillin skin testing with the major and minor determinants of penicillin can reliably identify persons at high risk for penicillin reactions (238,239). Although these reagents are easily generated and have been available for more than 30 years, only benzylpenicilloyl poly-L-lysine (Pre-Pen [i.e., the major determinant]) and penicillin G have been available commercially. These two tests identify an estimated 90%–97% of the currently allergic patients. However, because skin testing without the minor determinants would still miss 3%–10% of allergic patients and because serious or fatal reactions can occur among these minor-determinant-positive patients, caution should be exercised when the full battery of skin-test reagents is not available (Box 2). Manufacturers are working to ensure better availability of the Pre-Pen skin test reagent as well as an accompanying minor determinant mixture.

Recommendations

If the full battery of skin-test reagents is available, including both major and minor determinants (see Penicillin Allergy Skin Testing), patients who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Skin-test-positive patients should be desensitized before initiating treatment.

If the full battery of skin-test reagents, including the minor determinants, is not available, the patient should be skin tested using benzylpenicilloyl poly-L-lysine (i.e., the major determinant) and penicillin G. Patients who have positive test results should be desensitized. One approach suggests that persons with a history of allergy who have negative test results should be regarded as possibly allergic and desensitized. Another approach in those with negative skin-test results involves test-dosing gradually with oral penicillin in a monitored setting in which treatment for anaphylactic reaction can be provided.

If the major determinant (Pre-Pen) is not available for skin testing, all patients with a history suggesting IgE-mediated reactions to penicillin (e.g., anaphylaxis, angioedema, bronchospasm, or urticaria) should be desensitized in a hospital setting. In patients with reactions not likely to be IgE-mediated, outpatient-monitored test doses can be considered.

Penicillin Allergy Skin Testing

Patients at high risk for anaphylaxis, including those who 1) have a history of penicillin-related anaphylaxis, asthma, or other diseases that would make anaphylaxis more dangerous or 2) are being treated with beta-adrenergic blocking agents,

should be tested with 100-fold dilutions of the full-strength skin-test reagents before being tested with full-strength reagents. In these situations, patients should be tested in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, the patient should not have taken antihistamines recently (e.g., chlorpheniramine maleate or fexafenadine during the preceding 24 hours, diphenhydramine HCl during the preceding 4 days, or hydroxyzine or phenothiazines during the preceding 3 weeks).

Procedures

Dilute the antigens either 100-fold for preliminary testing (if the patient has had a life-threatening reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year).

Epicutaneous (Prick) Tests

Duplicate drops of skin-test reagent are placed on the volar surface of the forearm. The underlying epidermis is pierced with a 26-gauge needle without drawing blood. An epicutaneous test is positive if the average wheal diameter after 15 minutes is ≥ 4 mm larger than that of negative controls; otherwise, the test is negative. The histamine controls should be positive to ensure that results are not falsely negative because of the effect of antihistaminic drugs.

Intradermal Test

If epicutaneous tests are negative, duplicate 0.02-mL intradermal injections of negative control and antigen solutions are made into the volar surface of the forearm by using a 26- or 27-gauge needle on a syringe. The margins of the wheals induced by the injections should be marked with a ball point pen. An intradermal test is positive if the average wheal diameter 15 minutes after injection is >2 mm larger than the initial wheal size and also is >2 mm larger than the negative controls. Otherwise, the tests are negative.

Desensitization

Patients who have a positive skin test to one of the penicillin determinants can be desensitized (Table 1). This is a straightforward, relatively safe procedure that can be performed orally or IV. Although the two approaches have not been compared, oral desensitization is regarded as safer and easier to perform. Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions can occur. Desensitization usually can be completed in approximately 4–12 hours, after which time the first dose of penicillin is administered. After desensitization, patients must be maintained on penicillin continuously for the duration of the course of therapy.

Box 2. Skin-test reagents for identifying persons at risk for adverse reactions to penicillin*

Major Determinant

- Benzylpenicilloyl poly-L-lysine (PrePen) (AllerQuest, Plainville Connecticut) (6×10^{-5} M).

Minor Determinant Precursors†

- Benzylpenicillin G (10-2M, 3.3 mg/mL, 10,000 units/mL)
- Benzylpenicilloate (10-2M, 3.3 mg/mL)
- Benzylpenicilloate (or penicilloyl propylamine) (10-2M, 3.3 mg/mL)

Positive Control

- Commercial histamine for intradermal skin testing (1.0 mg/mL)

Negative Control

- Diluent (usually saline) or allergen diluent

* Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204–15. Reprinted with permission from G.N. Beall and *Annals of Internal Medicine*.

† Aged penicillin is not an adequate source of minor determinants. Penicillin G should be freshly prepared or should come from a fresh-frozen source.

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include discharge of mucopurulent or purulent material, dysuria, or urethral pruritis. Asymptomatic infections are common. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis (240–243). If clinic-based diagnostic tools (e.g., Gram-stain microscopy, first void urine with microscopy, and leukocyte esterase) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia. Further testing to determine the specific etiology is recommended because both chlamydia and gonorrhea are reportable to health departments and a specific diagnosis might improve partner notification and treatment. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of both *N. gonorrhoeae* and *C. trachomatis*. Culture and hybridization tests require urethral swab specimens, whereas NAATs can be performed on urine specimens. Because of their

higher sensitivity, NAATs are preferred for the detection of *C. trachomatis* (197).

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID) on urethral smear is indicative of gonorrhea infection, which is frequently accompanied by chlamydial infection. Nongonococcal urethritis (NGU), which is diagnosed when examination findings or microscopy indicate inflammation without GNID, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower burden of disease occurring among older men (244). Complications of NGU among males infected with *C. trachomatis* include epididymitis and Reiter's syndrome. Documentation of chlamydial infection is essential because of the need for partner referral for evaluation and treatment.

In most cases of nonchlamydial NGU, no pathogen can be detected. *M. genitalium*, which appears to be sexually transmitted, is associated with both symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States (240–243). *T. vaginalis*, HSV, and adenovirus also can cause NGU, but data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent (244–247). Diagnostic and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., contact with trichomoniasis, genital lesions, or severe dysuria and meatitis, which might suggest genital herpes) or when NGU is not responsive to therapy. Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse (244).

Confirmed Urethritis

Clinicians should attempt to obtain objective evidence of urethral inflammation. However, if clinic-based diagnostic tools (e.g., Gram-stain microscopy) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia.

Urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucopurulent or purulent discharge on examination.
- Gram stain of urethral secretions demonstrating ≥ 5 WBC per oil immersion field. The Gram stain is the preferred rapid diagnostic test for evaluating urethritis and is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing GNID.

TABLE 1. Oral desensitization protocol for patients with a positive skin test*

Penicillin V suspension dose [†]	Amount [§] (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Note: Observation period was 30 minutes before parenteral administration of penicillin.

* Reprinted with permission from the New England Journal of Medicine (Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 1985;312:1229–32.).

[†] Interval between doses, 15–30 minutes; elapsed time, 4–8 hours; cumulative dose, 1.3 million units.

[§] The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating ≥ 10 WBC per high-power field.

If none of these criteria are present, testing for *N. gonorrhoeae* and *C. trachomatis* using NAATs might identify additional infections (248). If the results demonstrate infection with either of these pathogens, the appropriate treatment should be given and sex partners referred for evaluation and treatment. If none of these criteria are present, empiric treatment of symptomatic males is recommended only for men at high risk for infection who are unlikely to return for a follow-up evaluation. Such patients should be treated with drug regimens effective against gonorrhea and chlamydia. Partners of patients treated empirically should be evaluated and treated, if indicated.

Nongonococcal Urethritis

Diagnosis

All patients who have confirmed or suspected urethritis should be tested for gonorrhea and chlamydia. Testing for chlamydia is strongly recommended because of the increased utility and availability of highly sensitive and specific testing methods (e.g., NAATs) and because a specific diagnosis might enhance partner notification and improve compliance with treatment, especially in the exposed partner.